g. Antibodies Against PD-1, Against PD-L1, or Against CTLA-4 for Treating Melanoma

The Robert trial and the Postow trial, along with another trial, the Weber trial, should be contemplated a bit further, because of the dramatic efficacy of the study drugs in melanoma clinical trials. Although it was mentioned above that "the median progression free survival was not reached" in one of the study arms, this was not because the trial was discontinued due to severe drug toxicity. Instead, the results of the clinical trial were analyzed and published prior to reaching median PFS, because it was obvious, at the early point in the trial, that the drug was working.

Dramatic efficacy was found in the following melanoma trials:

- *Weber trial*. Chemotherapy arm versus antibody arm [dacarbazine chemotherapy versus novilumab (anti-PD-1)] (59).
- *Robert trial*. First antibody arm versus second antibody arm [pembrolizumab (anti-PD-1) vs ipilimumab (anti-CTLA-4)] (60).
- *Postow trial*. Antibody monotherapy arm versus combination arm with two antibodies (ipilimumab vs ipilimumab plus nivolumab) (61).

Pembrolizumab is an anti-PD-1 antibody. Nivolumab is also an anti-PD-1 antibody. Ipilimumab is an anti-CTLA-4 antibody. It is self-evident that nivolumab and ipilimumab have different mechanisms of action, because they bind to different targets. Also, it might be expected that administering the combination of both antibodies to a melanoma patient will have an additive effect.

In the Weber trial—*chemotherapy* versus *antibody (anti-PD-1 antibody)*—objective response rate with chemotherapy was only 11%, while that with nivolumab was 32%.

In the Robert trial—*pembrolizumab* (anti-PD-1) versus *ipilimumab (anti-CTLA-4)*—that is, where each antibody bound to a different target, pembrolizumab had greater efficacy and produced an objective response rate of about 33% while, in contrast, ipilimumab was less effective, and produced an objective response rate of only 11.9%.

In the Postow trial—combination of *nivolumab plus ipilimumab* versus *ipilimumab only*—the combination had a greater efficacy, providing an objective response of 61%, and the ipilimumab monotherapy resulted in an objective response of only 11% (62).

Thus, it can be seen that in the three melanoma trials, chemotherapy was least effective, and the combination of nivolumab plus ipilimumab was the most effective.

h. Data on PFS can Present Earlier, and can be More Dramatic, Than Data on OS—The Slamon Study

In a clinical trial on breast cancer, Slamon et al. (63), treated women with surgery. After surgery, HER2 expression was measured on

[59]Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16:375–84.

[60]Robert C, Schacter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. New Engl. J. Med. 2015. http://dx.doi.org/10.1056/NEJMoa1503093 (12 pp.).

[61]Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. New Engl. J. Med. 2015. http://dx.doi.org/10.1065/NEJMoa1414428.

[62]Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. New Engl. J. Med. 2015. http://dx.doi.org/10.1065/NEJMoa1414428.

[63]Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. New Engl. J. Med. 2001;344:783–92.